

Gender Selection: Ethical, Scientific, Legal, and Practical Issues

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Purpose: This work offers an overview of the technology available and assisted reproductive technology (ART) practitioner attitudes to human reproductive sex preselection in either sperm with the use of flow cytometry (FC) or in embryos by means of preimplantational genetic diagnose (PGD) together with an analysis of Spanish legal environment.

Methods: A review of the legal, ethical and technical literature of the methods to select the sex in the offspring is performed.

Results: Sex selection in humans has different utilities to be employed depending on each country's law. Moreover, different ethical concerns are raised depending on the type of sex selection, in sperm or embryos. Both methodologies to pre-select the sex are trustworthy, with a high predictive power in the determination of the sex, but nevertheless, PGD is better than FC selection in this aspect.

Conclusions: After a careful analysis of ethical, legal, and scientific features of gender selection, FC combined with PGD appears to be the most acceptable way to select the sex of the progeny whatever the circumstances are.

KEY WORDS: Gender selection; sperm sex selection; preimplantational diagnose.

INTRODUCTION

The selection of the gender of the offspring has been a matter of scientific and nonscientific research for many years. Nevertheless, no technique has been demonstrated to be useful for this purpose until the advent of modern molecular procedures made available this possibility together with advanced techniques in assisted reproduction.

This was the reason that delayed the discussion about the convenience of gender selection until the recent years.

Technically, two approaches made this possibility available.

One of them is the preimplantational diagnose (PGD) of in vitro obtained embryos. To this end, six to eight cell embryos can be biopsied to obtain single blastomeres with the aim to determine sexual chromosomes of the embryo, by using specific probes that bind with either X or Y chromosomes (1).

The second option is to separate in an ejaculate the sperm cell population containing a concrete chromosome, with the help of modern flow cytometry (FC) techniques by staining the sperm nuclei with vital fluorescent stains that permitted the discrimination between X and Y carrying spermatozoa because of the slight differences in the total DNA content that they exhibited (2).

Once these methods were confirmed to be safe and reliable, their potential applications started an ethical conflict. Many topics regarding this issue must be

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addressed. Is the fact of selecting the gender of the progeny ethical when a sex-linked disease is not the reason? Is family balancing a reason enough and when is a family unbalanced? Are all the methods equally acceptable and efficient?

Within this review, our aim was to expose our point of view, as well as to describe the ethical and legal aspects to show an overview of the currently available techniques for sex preselection in the human.

TECHNICAL PROCEDURES

Until now, only two techniques are available to predetermine the gender in the offspring with good results: the preimplantational genetic diagnose and the flow cytometry sex selection in sperm. Both have been widely validated, and no deleterious effect has been described yet because of these treatments.

PGD consists in the genetic study of the embryo before it is replaced to the mother to implant. This possibility, unthinkable a few decades ago, has become available since fluorescent in situ hybridization and IVF techniques have been fully developed.

Briefly, the procedure consists in a common IVF cycle, with controlled ovarian hyperstimulation, where the embryos will be biopsied to obtain single blastomeres for study. In these cells we will determine their chromosomal content, and finally a decision will be taken about the convenience to transfer each embryo back to the mother depending on the results obtained (3).

Sex-linked diseases studies are the most frequent motives to perform embryo sexing. To date, more than 300 diseases have been related to the sexual chromosomes (4). In the third report of the ESHRE PGD consortium, a total of 2100 started cycles were reported, and X-linked diseases is the second indication of PGD after chromosomal abnormalities (5).

Sperm sex selection has been thought for a long period of time for different reasons, including the easiness to obtain the samples, and its utility in veterinary for food producing animals. Finally, it was employed in humans.

FC cell sorting of sperm was the method employed to augment the concentration of spermatozoa of the desired sex since other biophysical methods to differentiate between Y- or X-chromosome carrying spermatozoa were absolutely vain. The difference that invariably permit to distinguish between sperm carrying X- or Y-chromosome in their nuclei is the different quantity of total DNA.

The first successful separation by FC was carried out on the mouse, which shows total DNA content difference of 3.7% (6). This technique was applied to a commercial cell sorter by Johnson and Pinkel (7). This was followed by rabbit (8), and other animal species (9–12). In these works a healthy offspring was obtained in consecutive generations without teratogenic effect on the embryos or fetuses (13). In human sperm samples, the first work was done in 1993 (2).

Although many concerns have been raised regarding its safety, only healthy newborns have been reported to date, and studies from other groups tested the mutagenicity caused by the exposure to punctual UV light ray, as well as the employment of fluorochromes that bind DNA and were unable to find any detrimental effect on sperm (14,15).

ETHICAL AND PRACTICAL ISSUES

The main ethical problems raised against PGD procedures, apart from classical religious-moral inconvenient regarding embryo obtainment and manipulation is that lots of embryos will be created and never relocated into the mother if they are not of the appropriate sex.

No doubt must stay if the analysis confirms that the embryos will develop into humans with a concrete and known pathology, often very severe. Nevertheless, the predefined limits became unclear if only the condition of being carrier is transmitted. Then, under the patients' point of view, they should have the chance to decide about their children's future.

But what is new in comparison with the past is the first reference for social sexing or family balancing in the ESHRE PGD Consortium. These couples have no medical indication for sex determination, and therefore it's inappropriate to use the term "diagnosis" (5). If the sex selection by means of PGD analysis is chosen to equilibrate the "problem" of the presence of an unbalanced family, it surely will lead to an immense conflict in the public opinion; in fact, the majority of the centers that performed the PGD consortium were against this social sexing. There was also a lot of controversy regarding publication of these European anonymous data with some arguments in favor but mainly against it because some of the centers do not want to be associated with social sexing. In fact, an article of PGD for gender selection for family balancing in India has been published (16), and consecutive responses to this publication have been obtained before, which in big words were against it (17,18).

Also, FC system has some disadvantages, which must be analyzed before a treatment is planned.

First, regarding the semen samples, because of an important number of sperm cells is lost during the procedure, and a minimum number of total motile cells must be available. This limits the accessibility of these methods for all patients, when even the most severe male factors can be overcome by ICSI and the subsequent PGD.

Second, nowadays the only possibility to sort sperm depending on the sex is to achieve a collaboration with the World's patent owner MicroSort[®]. Independently of the economic aspects, this is a handicap for patients outside the United States of America, since the only possibilities are to freeze an important number of samples, or directly travel to the States in order to get the sperm sorted.

Moreover, the bureaucracy difficulties to import human semen in some countries produce big delays, and samples can get thawed, thus making this procedure extremely stressing and complicated for not citizens of the States.

Third, for its use in artificial insemination, or IVF without PGD, the patients must be advertised that 100% of pregnancies of the desired sex is not guaranteed, and this can be an important issue in the situations of family balancing.

In our opinion, in those couples where the prevention of a disease is not the cause to select the gender of their progeny, the futile creation of embryos that otherwise would develop into completely normal persons, PGD must be carefully analyzed.

The right solution must be a combination of both above-mentioned methods: First, a sperm enrichment on the desired sex followed by PGD confirmation would be the most appropriate way to select the sex in the progeny.

CONCLUSIONS

At the present time, the option of the election of the gender of the future children is available. The two methods that permit this have differences in their efficiency, and ethical problems that they can raise. A better solution is the adequate combination of both.

When the cause to select the gender is a sex-linked disease, this can reduce the probabilities to have undesired embryos, and we will have complete confirmation that the transmission of the disease has been ruled out.

In our experience, in PGD cycles, the highest number of embryos must be obtained to have enough to

select. If a low number is obtained, there is an important risk of having very few for selection, and, after that, to have no embryos of the adequate sex to be transferred. These parameters can be improved by a previous selection in sperm.

The future of the sex selection in these cases will be terminated when PCR techniques on single blastomeres to detect concrete mutations will be an established technique to confirm the presence of an altered genotype in the embryos.

Other main cause to select the sex of the progeny comprehends those fathers that already have children, with the aim to compensate their family with a representation of the other sex. Even the possibility to select the sex in the first child must be considered. We are favorable to the selection of sex for family balancing if some concerns are respected: 1) there should be a balance in the sex ratio within one center and within 1 year (as many cases for boys and girls); 2) between the healthy embryos of undesired sex must have the same chance to live than the other of the desired sex, then, the end of the embryos initially discarded should be donation; and 3) patients should always pay themselves for the treatment.

The only problem it raises is the possibility of an advanced age in the mother, maybe higher than the maximum allowed by law. Nevertheless, since the embryos have been chromosomically studied, any ethical concern must be ruled out.

In conclusion, no circumstance is reason enough to create embryos tagged as "forever frozen," or "only research-dedicated" because of a planned sex selection. To this end, the only way to act in these cases should be the FC method, since sperm cells will never be ethically as valuable as embryos. Moreover, we think that the patients must assume under their responsibility the possibility (although minor) that future children will not be of the desired sex.

In a recent questionnaire developed in our clinic, over more than 500 patients, approximately 85%, would pay one third more to have the possibility of choosing the sex of their child, even being the first born.

Within this population of patients, there were some cases with a sex unbalanced family, whose situation resulted stressing and were psychologically affected, thus confirming in some people that its use is at least as necessary as other medical therapies that lead to an improvement in the quality of life, for example, esthetics surgery.

In these cases we do not consider that the selection in the way that we recommended is a manner of

gender discrimination, given that no discrimination is possible among uncreated embryos. Moreover, for the same reason, this is not the beginning of the selection of children with concrete genetic characteristics.

Legally, these procedures are not allowed by Spanish Assisted Reproduction Law, which dates of 1988 (SARL 1988), since it is clearly expressed that the sex cannot be preselected. No mention of the methods or reasons is included. Surely, if attention to the public opinion and a careful analysis of the methods is paid, this situation could change in the next years.

Methodologically, the system to select the sex of future children is right now available. The only question remaining is to achieve a consensus to regulate its use, depending on moral and ethical issues of the three parts implicated: ART practitioners, patients or potential users, and finally the whole society.

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